REMARKS

The present application is directed to methods for detecting cancer by combining mammalian autoantibodies with a patient sample to determine whether cancer-associated marker proteins are present in the sample. The autoantibodies demonstrate a superior affinity for cancer-associated marker proteins, thereby enabling early cancer detection and the ability to commence treatment and enhance cancer patient survival.

Claims 2-4 and 52-66 are pending. Claims 1 and 5-51 were previously cancelled. Cancellation of these claims should not be considered a forfeiture of this subject matter, and applicants reserve the right to pursue the cancelled subject matter in divisional applications.

Priority Document

Applicants enclose herewith a certified copy of the priority document GB9827228.9.

Applicants note that the first sentence of the specification was previously amended in a Preliminary Amendment filed 8 June 2001 to insert reference to the PCT application and the enclosed priority document GB9827228.9.

Withdrawn Rejections under 35 U.S.C. §102

Applicants wish to thank the Examiner for withdrawing the rejection of Claims 1, 3, 4, 52-54 and 62-66 under 35 U.S.C. §102(b) on the basis that the amended claims are not anticipated by Rao *et al.* (*Am J. Obstet. Gynecol. July 1998, 159:94-98*; "Rao").

Rejections under 35 U.S.C. §103

Claims 2-4, 52-58, 61, 62 and 66 have been rejected under 35 U.S.C. §103(a) as being obvious over Petrakou *et al.* (*International Journal of Oncology*, 1997, vol. 11, suppl., page 902; Petrakou). Applicants respectfully traverse.

The claims are directed to a method of detecting a modified form of a wild-type cancer-associated protein marker (or breast cancer associated marker in Claims 55 and

66, or MUC1 in Claim 56) in a bodily fluid from a mammal having various stages of cancer using autoantibodies obtained from the mammal.

Applicants respectfully submit that the International Preliminary Examining Authority found the claimed method novel and non-obvious over the Petrakou reference. (Applicants apologize for the late submission of this reference, but assumed that the Petrakou reference had been cited in an Information Disclosure Statement with the filing of the present application because the International Search Report listing this document was included with the application when filed by former counsel.) A copy of the International Preliminary Examination Report is enclosed for the Examiner's convenience.

The comments of the PCT Examiner in the Preliminary Examination Report, dated 05/06/2001, are reproduced as follows:

> The present application (PA) appears to meet the requirements of Article 33(1) and (3) PCT, because the subject-matter of claims 1-51 appears to be new, inventive and industrially applicable in the sense of Article 33(1) – (3) and Rule 64 PCT.
> Document D1 is identified as the closest prior art. D1 discloses an *in vitro* method for detecting anti-MUC-1 autoantibodies in a sample of body fluid (e.g. a serum sample) using MUC1 antigen preparations (cf D1, abstract). The MUC1 antigen preparation of D1 may be normal urinary MUC1, protein associated MUC1, cancer-associated MUC1 or synthetic MUC1. The disclosure of the PA is based on the use of autoantibodies to detect the presence of a cancer-associated antigens (e.g. MUC1) in samples of body fluids; this is the immunological opposite of the method of D1. To this end, the PA surprisingly discloses that autoantibodies having specificity for cancer-associated antigens can be isolated from serum and subsequently used to detect the presence of cancer-associated antigen in a sample of body fluid. Furthermore, said autoantibodies show very low cross-reactivity with wild-type forms of cancer-associated antigens and possess far higher sensitivities than the antibodies currently used in tests to detect cancer-associate antigens.
> The artisan could find no indication for the above in the closest prior art D1 or any other prior art disclosed in the international search report or the description of D1.
> Benefit of the above is the ability to detect cancer-associated marker proteins from early stages of disease.
> In summary, as presently formulated novelty, inventivity and industrial applicability of the methods, reagents, cell lines and kits of claims 1-51 should apparently be recognized (cf. 33(1)-(3) and Rule 64 PCT).

Petrakou describes the use of MUC1 antigen preparations to detect the presence of anti-MUC1 autoantibodies in a serum sample for epitope mapping. However, the use of antigen preparations by Petrakou is the immunological opposite of the claimed method, which utilitizes autoantibodies to detect cancer-associated marker protein in a patient sample. Petrakou merely uses MUC1 proteins or peptides to confirm the existence of antibodies in the serum of advanced cancer patients and fails to suggest isolating autoantibodies and using them in any way in an assay.

Applicants respectfully submit that there is no suggestion that the autoantibodies detected in the assay of Petrakou could actually be purified from serum and then used as diagnostic reagents. Petrakou fails to contain any technical teaching as to how one might actually go about purifying autoantibodies for use as a reagent in an assay.

In addition, Petrakou fails to even imply that autoantibodies could be used to detect the presence of a cancer-associated marker protein in a sample. As set forth in the claims of the present application, the protein to be detected in the bodily fluid is a modified form of a wild-type protein. As appreciated by the PCT Examiner, Petrakou never even considers that autoantibodies could provide higher specificity than the antibodies currently used in tests to detect cancer-associate antigens. The data presented to the Examiner during the interview on October 7, 2004 and set forth in the Declaration Under 37 C.F.R. §1.132 by John Roberson (submitted with the Supplemental Amendment filed November 23, 2004), clearly demonstrated the specificity of autoantibodies in the claimed methods. As shown by the data (Figure 1) set forth in the previously submitted Declaration, autoantibodies were found to be more highly reactive with cancer-associated marker protein than with either normal or synthetic marker protein, thereby showing the specificity of autoantibodies to cancer-associated tumor marker protein. Likewise, data presented in the previously submitted Declaration showed that autoantibodies recognized cancer-associated marker protein significantly better than the monoclonal antibodies. In addition, the data demonstrated that the autoantibodies were highly specific for the cancer-associated protein and had little or no immunoreactivity with normal or synthetic peptides.

In summary, Petrakou neither suggests nor implies a diagnostic reagent composed of autoantibodies and certainly fails to recognize that autoantibodies are more specific than conventional monoclonal antibodies in that autoantibodies are able to distinguish between normal and cancer-associated marker proteins and autoantibodies display a higher affinity for cancer-associated protein, but little or no affinity for normal protein or synthetic peptides of the protein.

Accordingly, the claimed methods are non-obvious in view of Petrakou, and applicants respectfully request withdrawal of this rejection.

Claims 59, 60 and 63-65 have been rejected under 35 U.S.C. §103(a) as obvious over Petrakou as applied to Claims 2-4, 52-58, 61, 62 and 66 above, and further in view of Petrarca *et al.* (*European Journal of Cancer*, 32A:2155-2163, 1996; Petrarca). Applicants respectfully traverse.

Claims 59 and 60 are directed to an *in vitro* method for detecting a specific breast cancer-associated marker protein using autoantibodies, wherein the autoantibodies are obtainable from mononucleocytes isolated from a breast cancer patient. Claims 63 is directed to an *in vitro* method for detecting a cancer-associated marker protein using autoantibodies, wherein the autoantibodies are immobilized on a solid surface. Claim 64 depends from Claim 63 and is directed to an *in vitro* method for detecting a cancer-associated marker protein using autoantibodies, wherein complexes are detected using secondary antibodies carrying a detectable label or are detected using autoantibodies specific for at least one epitope of the marker protein. Claim 65 depends from Claim 63 and is directed to an *in vitro* method for detecting a cancer-associated marker protein using autoantibodies, further containing a labeled cancer-associated marker protein with an epitope recognized by the autoantibodies.

The Examiner agrees that Petrakou fails to teach the technical details of 1) making autoantibodies obtainable from mononucleocytes isolated from a patient with breast cancer, or 2) immobilizing antibody to a solid surface. However, the Examiner asserts that Petrarca disclose the production of autoantibodies from mononucleocytes and that Petrarca disclose the immobilization of antibodies to a solid support or a detection label.

As stated above, Petrakou fails to disclose an assay method using autoantibodies to detect circulating tumor markers in a patient sample nor would it be obvious to reverse this method to accomplish this task since there is no reasonable expectation of success that the autoantibodies in the patient sample could be isolated and used as an assay reagent in the same way. Petrarca fails to make up for these deficiencies, and therefore the combined references fail to disclose all of the elements of the claims to render the claimed methods obvious.

Claims 59 and 60 specify that the autoantibodies are obtainable from mononucleocytes isolated from a breast cancer patient. In contrast, the human antibodies isolated by Petrarca were obtained from the tumor-draining lymph nodes of ovarian cancer patients. (See page 2158, right column, lines 4-6.)

Claim 63 specifies that the autoantibodies are immobilized on a solid surface. In contrast, Petrarca immobilizes a 24mer synthetic peptide, or an unrelated synthetic peptide control, to the 96-well polystyrene plates. (See page 2156, right column, lines 4-11.) Therefore, Petrarca immobilizes antigen, not antibody.

Claim 64 specifies that the autoantibodies are immobilized on a solid surface and complexes are detected using secondary antibodies or secondary autoantibodies carrying a detectable label. The labeled secondary antibodies used by Petrarca are goat antimouse biotinylated secondary antibodies, not autoantibodies.

Claim 65 specifies that the autoantibodies are immobilized on a solid surface and further includes a labeled cancer-associated marker protein with an epitope recognized by the autoantibodies. Applicants can find no description in Petrarca of the use of such a labeled cancer-associated marker protein.

Furthermore, Petrarca's results describe human antibodies having different immunological characteristics from the murine monoclonal antibodies used in standard assays, thereby discouraging one of ordinary skill in the art from using autoantibodies in a detection assay. Figure 1b of Petrarca demonstrates the different epitope binding properties of human antibodies as compared to murine monoclonal antibodies, but fails to disclose whether this difference results in improved or reduced antigen binding over monoclonal

antibodies. One of ordinary skill could not predict how human antibodies would perform compared to murine monoclonal antibodies in an assay because of the difference in antigen binding domains. Petrarca discloses that the PPAH binding motif is distinct from the PDTR sequence, which is immunodominant. (p. 2158, col. 2). One of ordinary skill in the art would understand from this that murine monoclonal antibodies bind better and would therefore be better suited for a diagnostic assay. Petrarca further discloses that "all human antibodies are IgM" with weak reactivity and low affinity (p. 2161, col. 2). Petrarca therefore teaches away from applicants' findings of autoantibody high affinity and specificity. One of ordinary skill would not be motivated to use autoantibodies because, based on the teaching of Petrarca, there is no expectation that they would perform better than murine monoclonal antibodies in a detection assay. In the Declaration by Dr. John Robertson dated November 20, 2004, the data demonstrated that the autoantibodies provide an improved assay because of their increased sensitivity and affinity. This is unexpected in view of the negative teachings of Petrarca.

Absent the teachings of the present specification, there would be no reasonable expectation of success that autoantibodies could be used in an assay to detect a cancer-associated target antigen in a patient sample with such specificity and sensitivity. Applicants teach that autoantibodies outperform the conventional monoclonal antibody assays, which were the standard, and provide improved binding characteristics resulting in a highly sensitive and sensitive method for the detection of cancer-associated markers.

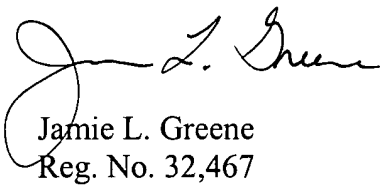
In view of at least the foregoing, the claimed methods are non-obvious over Petrakou in view of Petrarca, and applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants submit that the pending claims define novel and patentable subject matter and provide a complete response to the Office Action. Accordingly, applicants respectfully request allowance of these claims. No additional fees are believed due, however, the Commissioner is hereby authorized to charge any deficiencies which may be required, or credit any overpayment, to Deposit Account Number 11-0855.

Early and favorable consideration is earnestly solicited. If the Examiner believes any informalities remain in the application that can be resolved by telephone interview, a telephone call to the undersigned attorney is earnestly solicited.

Respectfully submitted,



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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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Verulam Gardens
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London WC1X 8BT
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	05. 06. 2001
Applicant's or agent's file reference SCB/51598001	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/04182	10/12/1999	10/12/1998

Applicant
THE UNIVERSITY OF NOTTINGHAM et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the International application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04182

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-20 as originally filed

Claims, No.:

1-51 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-51
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-51
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-51
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

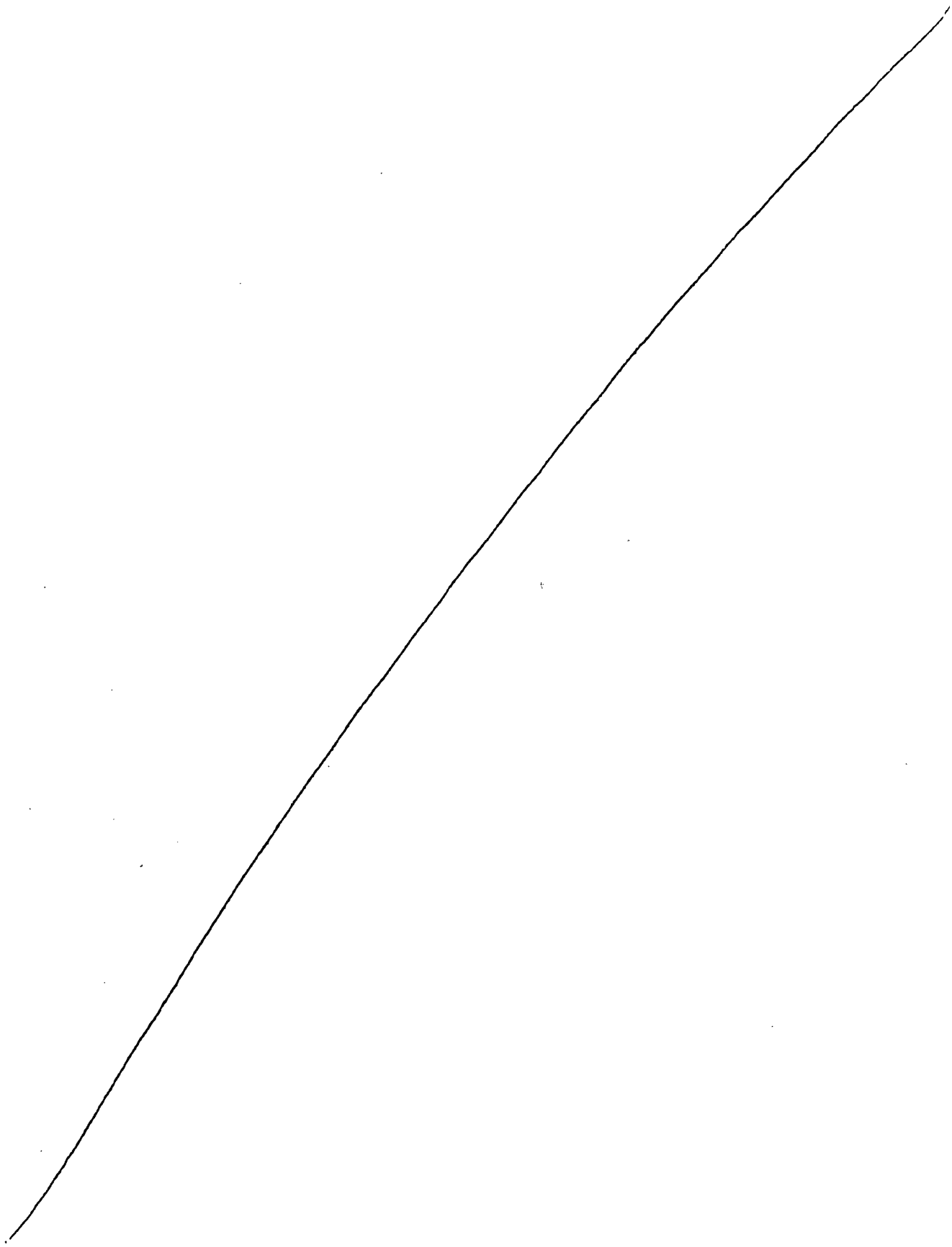
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet



Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document, which has been cited in the international search report:

D1: E. Petrakou et al. (1997). Preliminary studies on the binding of human autoantibodies to the MUC1 antigen. International Journal of Oncology, (1997) Vol. 11, No. SUPPL., pp. 902.

The present application (PA) appears to meet the requirements of Article 33(1) and (3) PCT, because the subject-matter of claims 1 -51 appears to be new, inventive and industrially applicable in the sense of Article 33(1) - (3) and Rule 64 PCT.

Document D1 is identified as the closest prior art. D1 discloses an *in vitro* method for detecting anti-MUC1 autoantibodies in a sample of body fluid (e.g. a serum sample) using MUC1 antigen preparations (cf D1, abstract). The MUC1 antigen preparation of D1 may be normal urinary MUC1, protein associated MUC1, cancer-associated MUC1 or synthetic MUC1. The disclosure of the PA is based on the use of autoantibodies to detect the presence of a cancer-associated antigens (e.g. MUC1) in samples of body fluids; this is the immunological opposite of the method of D1. To this end, the PA surprisingly discloses that autoantibodies having specificity for cancer-associated antigens can be isolated from serum and subsequently used to detect the presence of cancer-associated antigen in a sample of body fluid. Furthermore, said autoantibodies show very low cross-reactivity with wild-type forms of cancer-associated antigens and possess far higher sensitivities than the antibodies currently used in tests to detect cancer-associated antigens.

The artisan could find no indication for the above in the closest prior art D1 or any other prior art disclosed in the international search report or the description of D1.

Benefit of the above is the ability to detect cancer-associated marker proteins from early stages of disease.

In summary, as presently formulated novelty, inventivity and industrial applicability of the methods, reagents, cell lines and kits of claims 1-51 should apparently be recognized (cf. 33(1)-(3) and Rule 64 PCT).

Re Item VI
Certain documents cited

Depending on whether or not the present application validly claims a priority date earlier than the international filing date, the following document, which was cited in the international search report, might be considered in the course of further procedures.

WO-A-9958978 (UNIVERSITY OF NOTTINGHAM)

Re Item VII
Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII
Certain observations on the international application

1. Claims 2 and 48-51 are not clear ex art. 6 PCT, because the quantitative term "substantially" is not clear; the artisan would not automatically understand which degree or quantity is intended.

2. Claims 47-51 are not clear ex art. 6 PCT, because the phrase "as described herein with reference to the accompanying examples" is not clear; the artisan would not automatically understand which method (cf. claim 48), kit (cf. claim 49), reagent (cf. claim 50) or cell population (cf. claim 51) is intended.

3. Regarding to use of separate independent claims relating to the same subject-matter the following.

a. Although claims 1 and 48 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter. It would appear that conciseness and clarity ex art. 6 PCT could be enhanced by defining the relevant subject-matter in terms of a single independent claim, followed by dependent claims covering features which are merely optional.

b. The above also applies to claims 20 and 50.

c. The above also applies to claims 30 and 51.

d. The above also applies to claims 40 and 49.